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(21) International Application Number: PCT/GB98/03209 (22) International Filing Date: 27 October 1998 (27.10.98) (30) Priority Data: 9722682.3                      27 October 1997 (27.10.97)                      GB (71) Applicant (for all designated States except US): R.P. SCHERER CORPORATION [US/US]; 2301 West Big Beaver Road, Troy, MI 48007-7060 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): SEAGER, Harry [GB/GB]; Ashley Lodge, Ashley, Box, Corsham, Wiltshire SN14 9AN (GB). (74) Agent: HITCHCOCK, Esmond, Antony; Lloyd Wise, Tregear & Co., Commonwealth House, 1-19 New Oxford Street, London WC1A 1LW (GB).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  Published With international search report.	

(4) Title: SOLID DISPERSING VACCINE COMPOSITION FOR ORAL DELIVERY

## (7) Abstract

An oral vaccine is disclosed in which the vaccine composition and an adjuvant are carried on a fast-dispersing dosage form. The vaccines are targeted towards mucosal tissue, and the adjuvant serves to ensure sufficient residence time for the vaccine composition on the mucosal tissue to facilitate its absorption thereby.

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## SOLID DISPERSING VACCINE COMPOSITION FOR ORAL DELIVERY

This invention relates to pharmaceutical products, and particularly to such products suitable for oral ingestion and capable of rapid disintegration in the oral cavity.

5       A large variety of dosage forms for oral ingestion are known and readily available. Such dosage forms are used for the controlled delivery of medicaments to different parts of the body, the requisite control being achieved by the rate at which the carrier for the  
10       medicament breaks down and releases it. Thus, fast dispersing carriers are used for such products in which the medicament is to be quickly released. Slower dispersing carriers and carriers resistant to digestion by gastro-intestinal tract glands can be are used where  
15       it is intended that release of the medicament is to be delayed, for example until the product has itself reached the stomach or lower intestine.

Vaccines, which are important in prophylaxis against disease, exert their effects by provoking an  
20       immune response, the effect of which is to prevent re-infection by the challenging organism, or the onset of the disease process which would otherwise occur when the antigen against which the immune response has been provoked again challenges a sensitive tissue.

25       Most existing vaccines are delivered by injection, which is traumatic, inconvenient, expensive, and may fail to induce an appropriate immunogenic response in the mucosal tissues. Delivery by injection does not of course directly target the mucosal surfaces.

30       The present invention is directed at the use of oral dosage forms of the kind described above to carry vaccines to sites in the human or animal body where they can be best absorbed in a manner which promotes an immune response. According to the invention, a vaccine  
35       composition comprising an immunogenic amount of an antigenic preparations and an adjuvant is provided in a

solid dosage form for oral administration, the dosage form being capable of rapid disintegration. After disintegration the components of the dosage form rapidly coat and are retained in contact with the mucosal tissues of the buccopharyngeal region, to include mucosal associated lymphoid tissue. This brings the antigenic components in contact with tissues capable of absorption of the antigen. The dosage forms further incorporate adjuvants which either serve to enhance the absorption of the vaccine or to potentiate the immunogenic response upon absorption. It is preferred that compositions of the invention disintegrate within 1 to 60 seconds, more preferably 1 to 30 seconds, especially 1 to 10 seconds and particularly 2 to 8 seconds, of being placed in the oral cavity. Normally, the disintegration time will be less than 60 seconds following the disintegration method specified in United States Pharmacopoeia No. 23, 1995, in water at 37°C. Longer disintegration times may be needed if bioadhesive polymers are used to extend the residence time. However, normally disintegration within one minute should be possible.

80% of infections affect, or start, in the mucosal surfaces. Active immunisation against these infective agents may depend on the successful induction of a mucosal immune response. Successful mucosal vaccines could both protect the secretory surfaces- mucosal immunity, and also induce systemic immunity by induction of circulatory antibodies. They also have the benefit of ease of administration and lower costs. The induction of mucosal immunity is evidenced by the appearance of immunoglobulin A antibodies (IgA) in the mucous overlying the mucosa. Successful local stimulation of the mucosal membrane system produces a barrier against a specific pathogen, but this adaptive immunity also confers protection to mucous membranes at other sites in the body. Potentially, oral vaccines can

be used to induce immunity against oral, respiratory, genital and ocular pathogens. This ability to generate immunity at sites in the body away from the point of original antigenic stimulation has led to the concept of a common mucosal immune system. There are further indications that stimulation of the mucosal immune system can induce protective circulatory antibodies in the systemic immune system particularly IgG antibodies.

Vaccines delivered orally could stimulate nasal associated lymphoid tissue in the mouth and nasal pharyngeal area - the lymph nodes, tonsils and adenoids, and the gut associated lymphoid tissue in the Peyer's patches in the small intestine. Figure 1 appended hereto illustrates the location of these tissues.

Vaccines incorporate antigens which can be peptides, proteins or whole or partial fragments or extracts of bacterial or viral cells often attenuated to remove toxic components. A primary problem in vaccination procedures is ensuring that these antigens or antigenic compounds reach the appropriate site in sufficient quantities to provoke the requisite immune response.

There are two elements of the immune system which can provide the requisite immune response when stimulated by an antigen in a vaccine system. These are the systemic immune system and the mucosal immune system. The latter consists of areas of lymphoid tissue located in the gastrointestinal tract, the respiratory tract, the genitourinary tract, and the membranes surrounding sensory organs, and it is with this immune system that the present invention is particularly concerned. We have found that these areas of lymphoid tissue are very effectively targeted by antigens carried on a water dispersable matrix placed on the tongue. Such localised areas of lymphoid tissue, when activated by an absorbed antigen, secrete immunoglobulin A (IgA), which exerts an important function in mucosal immunity.

Secretory IgA molecules resist proteolysis and mediate antibody-dependant T cell mediated cytotoxicity; inherent microbial adherence, colonisation and penetration, as well as food antigen uptake. Stimulation of mucosal tissue can also result in secretion of circulatory IgG antibodies and in turn, IgM and IgE antibodies.

The principal function of the cells forming the lymphoidal tissue is to prevent absorption of pathogens and toxins or to inactivate these pathogens and toxins upon absorption to mucosal tissue. Generally considerably higher doses of antigens are required for mucosal immunisation, especially by the oral route. This is due to the existence of effective mechanical and chemical barriers, and the degradation and digestion of antigens by enzymes and acids. Additionally, there is a rapid clearance of material from the upper respiratory and digestive tracts to the stomach by mucociliary, peristaltic and secretory processes.

Rapidly dispersing oral administered dosage forms can be taken without water and disperse in very small volumes of saliva. This increases the coating of mucosal tissues containing the tonsillar associated lymphoid tissue and increases the residence time of antigens with these tissues. Some fast dispersing dosage forms are inherently mucoadhesive but residence time in contact with the target tissue could be further enhanced by the incorporation of a specific mucoadhesive. Suitable mucoadhesives are detailed in European patent application 92109080.9 and include:

- polyacrylic polymers such as carbomer and carbomer derivatives (Polycarbophil, Carbopol etc);
- cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC) and sodium

carboxymethylcellulose (NaCPC);

natural polymers such as gelatin, sodium alginate, pectin;

5

Suitable commercial sources for representative bioadhesive polymers include:

Carbopol acrylic copolymer - BF Goodrich Chemical Co., Cleveland, OH, USA

10

HPMC - Dow Chemical Co., Midland, MI, USA

HEC (Natrosol) - Hercules Inc., Wilmington, DE, USA

HPC (Kluoel) - Dow Chemical Co., Midland, MI, USA

MaCMC - Hercules, Inc., Wilmington, DE, USA

Gelatin - Deamo Chemical Corp., Elmford, NY, USA

15

Sodium Alginate - Edward Mandell Co., Inc., Carmel, NY, USA

Pectin - BDH Chemicals Ltd., Poole, Dorset, UK

Polycarbophil - BF Goodrich Chemical Co., Cleveland, OH, USA

20

The rapid dissolving dosage form promotes delivery of the vaccine to the target site, and the mucoadhesive system can be designed to maintain the vaccine in contact with the target mucosal lymphoid tissues in the mouth and pharynx, and to increase the residence time of the vaccine element at these potential surfaces for absorption. As a product for oral ingestion, from which the vaccine is quickly released once the product is taken, high concentrations of vaccine can thus be quickly delivered to the desired target sites.

25

30

Adjuvants are used to enhance absorption of the antigen at the target lymphoid tissue and/or to potentiate the immune response resulting from this absorption and stimulation. Suitable adjuvants can include the following:

35

Aluminium salts, non-toxic bacterial fragments, cytokines, cholera toxin (and detoxified fractions

thereof), Chitosan, Homologous heat-labile of  
E.coli (and detoxified fractions thereof),  
Lactide/glycolide homo + and copolymers (PLA/GA),  
Polyanhydride e.g. trimellitylimido-L-tyrosine,  
5 DEAE-Dextran, Saponins complexed to membrane  
protein antigens (immune stimulating complexes -  
ISCMS), Bacterial products such as  
lipopolysaccharide (LPS) and Muramyl dipeptide,  
(MDP), Liposomes, Cochleates, Proteinoids,  
10 Cytokines (Interleukins, interferons), Genetically  
engineered live microbial vectors, Non-infectious  
pertussis mutant toxin, Neurimidase/Galactose  
oxidase, Attenuated bacterial and viral toxins  
derived from mutant strains.

15 In some preferred embodiments of the invention the  
vaccine can be part of a microsphere which may be  
biodegradable. This microsphere material itself may act  
as an adjuvant or may be used in conjunction with other  
adjuvants. The vaccine element can be absorbed or  
20 incorporated onto or into microspheres, rendering it  
available for absorption into the lymphoid tissue  
effectively as soon as the tissue is ready to receive  
it. Suitable microspheres are formed from biodegradable  
polymeric materials. Particularly suitable are  
25 hydrophobic materials such as poly(lactic acid) and  
poly(lactide-co-glycide) polymers, and latex copolymers.  
These polymeric materials also confer resistance to  
enzymatic and hydrolytic digestion until their  
absorption into lymphoid tissue where the antigen can  
30 exert its immunogenic effect. They are preferentially  
made of hydrophobic materials which enhance absorption  
into the target tissues.

Fast dispersing dosage forms, delivered orally,  
have been demonstrated to rapidly disperse and coat the  
35 mucosal surfaces in the mouth and pharynx, where the  
mucosal associated lymphoid tissues are localised. In  
this respect reference is directed to a paper by Wilson



et al published in the International Journal of  
Pharmaceutics, 40 (1997) pages 119-123. Figure 1 in  
that paper shows the results of a gamma scintigraphic  
study. Dosage forms which dissolve rapidly in saliva,  
5 without the aid of water, have also been demonstrated to  
increase the time in which the rapidly dispersed  
contents are in contact with the target lymphoid tissue  
within the buccopharyngeal area and increase the time  
taken to reach the stomach, when compared to tablets and  
10 capsules. Reference is directed to a further paper by  
Wilson et al published in the International Journal of  
Pharmaceutics, 46 (1998) pages 241-246); see  
particularly Figure 1.

The use of a fast-dispersing dosage form, delivered  
15 orally, improves the targeting of vaccines to  
susceptible lymphoid tissues in the mouth and the  
pharynx, and in turn, the concentration of vaccine  
making contact with these tissues. Fast-dispersing  
dosage forms increase the contact time of vaccines with  
20 the susceptible lymphoid tissue in the buccopharyngeal  
area. Furthermore, where antigens are appropriately  
protected from digestion in the stomach and gut, rapidly  
dispersed antigenic materials will further target the  
lymphoid tissue in the Peyer's patches in the small  
25 intestine.

One example of a fast-dispersing dosage form is  
described in U.S. Patent No. 4855326 in which a melt  
spinnable carrier agent, such as sugar, is combined with  
an active ingredient and the resulting mixture spun into  
30 a "candy-floss" preparation. The spun "candy-floss"  
product is then compressed into a rapidly dispersing,  
highly porous solid dosage form.

U.S. Patent No. 5120549 discloses a fast-dispersing  
matrix system which is prepared by first solidifying a  
35 matrix-forming system dispersed in a first solvent and  
subsequently contacting the solidified matrix with a  
second solvent that is substantially miscible with the

first solvent at a temperature lower than the solidification point of the first solvent, the matrix-forming elements and active ingredient being substantially insoluble in the second solvent, whereby  
5 the first solvent is substantially removed resulting in a fast-dispersing matrix.

U.S. Patent No. 5079018 discloses a fast-dispersing dosage form which comprises a porous skeletal structure of a water soluble, hydratable gel or foam forming  
10 material that has been hydrated with water, rigidified in the hydrated state with a rigidifying agent and dehydrated with a liquid organic solvent at a temperature of about 0°C or below to leave spaces in place of hydration liquid.

Published International Application No. WO 93/12769 (PCT/JP93/01631) describes fast-dispersing dosage forms of very low density formed by gelling, with agar, aqueous systems containing the matrix-forming elements and active ingredient, and then removing water by forced  
15 air or vacuum drying.

U.S. Patent No. 5298261 discloses fast-dispersing dosage forms which comprise a partially collapsed matrix network that has been vacuum-dried above the collapse temperature of the matrix. However, the matrix is  
25 preferably at least partially dried below the equilibrium freezing point of the matrix.

Published International Application No. WO 91/04757 (PCT/US90/05206) discloses fast-dispersing dosage forms which contain an effervescent disintegration agent  
30 designed to effervesce on contact with saliva to provide rapid disintegration of the dosage form and dispersion of the active ingredient in the oral cavity.

U.S. Patent No. 5595761 discloses a particulate support matrix for use in making a rapidly dissolving  
35 tablet, comprising;

a first polypeptide component having a net charge when in solution, e.g. non-hydrolysed gelatin;

a second polypeptide component having a net charge of the same sign as the net charge of the first polypeptide component when in solution e.g. hydrolysed gelating; and

5 a bulking agent, and wherein the first polypeptide component and the second polypeptide component together comprise about 2% to 20% by weight of the particulate support matrix and wherein the bulking agent comprises about 60% to 96% by weight of the particulate support  
10 matrix; and

wherein the second polypeptide component has a solubility in aqueous solution greater than that of the first polypeptide component and wherein the mass: mass ratio of the first polypeptide component to the second  
15 polypeptide component is from about 1 :  $\frac{1}{2}$  to about 1 : 14; and

wherein when the support matrix is introduced into an aqueous environment the support matrix is disintegrable within less than about 20 seconds.

20 US Patent No. 5576014 discloses fast-dispersing dosage forms which dissolve intrabuccally and which comprise compressed moldings formed from granules comprising a saccharide having low moldability which has been granulated with a saccharide having high  
25 moldability. The resulting compressed moldings show quick disintegration in the buccal cavity.

EP-B-0690747 describes particles comprising an excipient forming a matrix and at least one active ingredient uniformly distributed in the mass of the  
30 matrix which are prepared by a process comprising the steps of preparing an homogeneous pasty mixture with a viscosity below 1 Pa.s, measured at room temperature (15-20°C), from at least one active ingredient, a physiologically acceptable hydrophilic excipient and  
35 water; extruding the resulting homogenous mixture and cutting the extrudate to give moist particles; freezing the resulting particles as they fall under gravity

through a stream of inert-gas at a temperature below 0°; and drying the particles by freeze drying.

Australian Patent No. 666666 discloses a rapidly disintegratable multiparticulate tablet having a mixture of excipients in which the active substance is present in the form of coated microcrystals or optionally coated microgranules. Such tablets disintegrate in the mouth in an extremely short time, typically less than 60 seconds.

US Patent No. 5382437 discloses a porous carrier material having sufficient rigidity for carrying and administering an active material which is capable of rapid dissolution by saliva and which is formed by freezing a liquified ammonia solution comprising liquid ammonia, a liquid ammonia-soluble gel or foam material and a rigidifying agent for the gel or foam material selected from the group consisting of a monosacchanide, a polysacchanide and combinations thereof, and deammoniating the frozen material thus formed by causing material transfer of ammonia from the frozen state to the gas state thereby leaving spaces in the carrier material in place of the frozen ammonia.

Published International Application No. WO 93/13758 (PCT/US92/07497) describes tablets of increased physical strength which disintegrate in the mouth in less than 10 seconds and which are prepared by combining and compressing a meltable binder, excipients and a pharmaceutically active agent into a tablet, melting the binder in the tablet and then solidifying the binder.

US Patents Nos. 3885026 and 4134943 also disclose fast-dispersing porous tablets and a method for increasing their physical strength by first compressing the tablet and then volatilising a readily volatilisable solid adjuvant incorporated in the tablet to attain the desired porosity.

EP-A-0601965 describes a shearform matrix material which can be used, inter alia, to deliver a

pharmaceutically active agent. The shearform matrix is formed by increasing the temperature of a feedstock which includes a solid non-solubilised carrier material to the point where it will undergo internal flow with the application of a fluid shear force, ejecting a stream of the heated feedstock thus formed under pressure from an orifice and then subjecting the feedstock to disruptive fluid shear force which separates the flow of feedstock into multiple parts and transforms the morphology of the feedstock.

US Patent No. 5683720 discloses discrete particles containing a pharmaceutically active agent which can be fast-dispersing and are formed by subjecting a solid, organic feedstock to liquiflash conditions whereby the feedstock is transformed instantaneously from solid to liquiform to solid, liquiform being a transient condition in which the feedstock has substantially unimpeded internal flow. Shear force is then imparted to the liquiform feedstock in an amount sufficient to separate tiny masses of feedstock which then solidify as discrete particles.

US Patent No. 5576014 discloses fast-dispersing dosage forms in the form of intrabuccally dissolving compressed mouldings comprising a saccharide having low mouldability which has been granulated with a saccharide having high mouldability.

Published International Application No. WO 95/34293 describes the preparation of fast-dispersing dosage forms comprising a three-dimensional crystalline-based porous network bound together to form a stable structure which is formed by mixing uncured shearform matrix and an additive, moulding the dosage form and curing the shearform matrix.

EP-A-0737473 discloses fast-dispersing dosage forms which are effervescent. Each such dosage form comprises a mixture of at least one water or saliva activated effervescent agent and a plurality of microcapsules

containing the active ingredient.

US Patent No. 5587180 describes fast-dispersing dosage forms which include an active ingredient and a particulate support matrix comprising a first polymeric component which may be a polypeptide such as a non-hydrolysed gelatin, a second polymeric component which may be a different polypeptide such as a hydrolysed gelatin and a bulking agent. Generally, the dosage forms are prepared by mixing the particulate support matrix with the active ingredient and any other additives and then forming the mixture into tablets by compression.

EP-A-0627218 discloses a fast-dispersing dosage form which comprises a tablet comprising a sugar alcohol or the like as principal ingredient which is prepared by the wet granulation method in which a kneaded mixture of the sugar alcohol or the like with a drug is compression molded before drying.

Published International Application No. WO 94/14422 describes a process for drying frozen discrete units in which the solvent is removed under conditions whereby the solvent is evaporated from the solid through the liquid phase to a gas, rather than subliming from a solid to a gas as in lyophilisation. This is achieved by vacuum drying at a temperature below the equilibrium freezing point of the composition at which point the solvent (such as water) changes phase.

The term "fast-dispersing dosage form" refers to compositions which disintegrate/disperse within 1 to 60 seconds, preferably 1 to 30 seconds, more preferably 1 to 10 seconds and particularly 2 to 8 seconds, of being placed in the oral cavity. It therefore encompasses all the types of dosage form described in the preceding paragraphs as well as any other equivalent dosage form. However, it is particularly preferred that the fast-dispersing dosage form is of the type described in U.K. Patent No. 1548022, that is, a solid fast-dispersing

dosage form comprising a network of the active ingredient and a water-soluble or water-dispersible carrier which is inert towards the active ingredient, the network having been obtained by subliming solvent  
5 from a composition in the solid state, that composition comprising the active ingredient and a solution of the carrier in a solvent.

In the case of the preferred type of fast-dispersing dosage form described above, the composition  
10 will preferably contain, in addition to the active ingredient, matrix forming agents and secondary components. Matrix forming agents suitable for use in the present invention include materials derived from animal or vegetable proteins, such as the gelatins;  
15 dextrans and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan; polysaccharides; alginates; carboxymethylcelluloses; carrageenans; dextrans; pectins; synthetic polymers such as polyvinylpyrrolidone; and polypeptide/protein or  
20 polysaccharide complexes such as gelatin-acacia complexes.

Other matrix forming agents suitable for use in the present invention include sugars such as mannitol, dextrose, lactose, galactose and trehalose; cyclic  
25 sugars such as cyclodextrin; inorganic salts such as sodium phosphate, sodium chloride and aluminium silicates; and amino acids having from 2 to 12 carbon atoms such as a glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine  
30 and L-phenylalanine.

One or more matrix forming agents may be incorporated into the solution or suspension prior to solidification. The matrix forming agent may be present  
in addition to a surfactant or to the exclusion of a  
35 surfactant. In addition to forming the matrix, the matrix forming agent may aid in maintaining the dispersion of any active ingredient within the solution.

or suspension. This is especially helpful in the case of active agents that are not sufficiently soluble in water and must, therefore, be suspended rather than dissolved.

5       Secondary components such as preservatives, antioxidants, surfactants, viscosity enhancers, colouring agents, flavouring agents, pH modifiers, sweeteners or taste-masking agents may also be incorporated into the composition. Suitable colouring  
10       agents include red, black and yellow iron oxides and FD & C dyes such as FD & C blue No. 2 and FD & C red No. 40 available from Ellis & Everard. Suitable flavouring agents include mint, raspberry, liquorice, orange, lemon, grapefruit, caramel, vanilla, cherry and grape  
15       flavours and combinations of these. Suitable pH modifiers include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Suitable sweeteners include aspartame, acesulfame K and thaumatic. Suitable taste-masking agents include sodium  
20       bicarbonate, ion-exchange resins, cyclodextrin inclusion compounds, adsorbates or microencapsulated actives.

The present invention might for example, be used for the delivery of vaccines designed to prevent or reduce the symptoms of diseases of which the following  
25       is a representative but not exclusive list:

Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera, Herpes, Typhoid, HIV, AIDS, Measles, Lyme disease, Travellers' Diarrhoea,  
30       Hepatitis A, B and C, Otitis Media, Dengue Fever, Rabies, Parainfluenza, Rubella, Yellow Fever, Dysentery, Legionnaires Disease, Toxoplasmosis, Q-Fever, Haemorrhagic Fever, Argentina Haemorrhagic Fever, Caries, Chagas Disease, Urinary Tract  
35       Infection caused by E.coli, Pneumococcal Disease, Mumps, and Chikungunya.

It can be used to prevent or reduce the symptoms of



other disease syndromes of which the following is a representative but not exclusive list of causative organisms:

5       Vibrio species, Salmonella species, Bordetella  
species, Haemophilus species, Toxoplasmosis gondii,  
Cytomegalovirus, Chlamydia species, Streptococcal  
species, Norwalk Virus, Escherischia coli,  
Helicobacter pylori, Rotavirus, Neisseria  
gonorrhoeae, Neisseria meningitidis, Adenovirus,  
10       Epstein Barr Virus, Japanese Encephalitis Virus,  
Pneumocystis carini, Herpes simplex, Clostridia  
species, Respiratory Syncytial Virus, Klebsiella  
species, Shigella species, Pseudomonas aeruginosa,  
Parvovirus, Campylobacter species, Rickettsia  
15       species, Varicella zoster, Yersinia species, Ross  
River Virus, J.C. Virus, Rhodococcus equi,  
Moraxella catarrhalis, Borrelia burgdorferi and  
Pasteurella haemolytica.

20       The invention can also be used with vaccines  
directed to non-infections immuno-modulated disease  
conditions such as topical and systematic allergic  
conditions such as Hayfever, Asthma, Rheumatoid  
Arthritis and Carcinomas.

25       Prospective vaccines for veterinary use include  
those directed to Coccidiosis, Newcastle Disease,  
Enzootic pneumonia, Feline leukaemia, Atrophic rhinitis,  
Erysipelas, Foot and Mouth disease, Swine, pneumonia,  
and other disease conditions and other infections and  
auto-immune disease conditions affecting companion and  
30       farm animals.

35       In a preliminary test the immunogenicity of tetanus  
toxoid (TT) in twenty-five rabbits was studied following  
oral delivery in fast dispersing dosage forms (FDDF) of  
the kind described in British Patent No. 1,548,022. As  
references, similar tests were conducted using oral  
administration of TT in solution and intramuscular  
administration by injection of TT adsorbed to aluminium.

hydroxide. The administered formulations are set out in Table 1 in which the TT concentration is suppressed as the concentration of TT protein. The adjuvants used in formulations 1 to 3, PLSP and Chitosan, are discussed in more detail in published Patent Specification Nos.

WO97/02810 and WO90/09780. A summary of the dose groups is given in Table 2. Oral administration of formulations Nos 1 to 3 was by placement of the FDDF unit at the rear of the tongue after spraying the oral cavity with

0.12ml. of UHP water after which the oral cavity was again sprayed with 0.06ml. of UHP water. Formulation 4 was delivered in a dose of 0.5ml by syringe delivered to the rear of the tongue. Formulation 5 was delivered by injection of a 0.2ml dose to the quadriceps (front thigh) to muscles of the left hind limb. Prior to each dose administration, and at termination blood and saliva samples were collected. The dosing and sampling schedule is set out in Table 3.

Figure 2 is a block diagram showing the geometric mean titre values of total IgA antibodies in saliva samples after administration of TT in the various formulations of Table 1 above (mean  $\pm$  SD). As can be seen from the diagram (the ordinate is on a logarithmic scale) the peak IgA values achieved using formulations 1 to 3 are significantly better than those for formulation 5 with formulation 1 providing the best figures by a considerable margin. Similar tests were conducted to monitor TT specific antibodies. The results are illustrated in Figure 3. Even on a lower logarithmic scale formulations 1 and 2 show significant improvement in immune response relative to the intramuscular delivered dosage, formulations 5.

It should be noted that only saliva samples that exhibited a positive response to the assay text were recorded. This explains the apparent absence of any immune response at some stages for some formulations, and the apparent absence of response at any stage for

formulation 4. The tests showed some response at these stages, but not any that were felt to be statistically significant. We were satisfied on the basis of these tests that the improved immune response exhibited by formulations 1 and 2 in Figure 3 demonstrates the potential benefit of administering vaccines with one or more adjuvants in a fast dispensing dosage form, by oral delivery.

CLAIMS

1. A vaccine composition comprising an immunogenic amount of an antigenic preparations and an  
5 adjuvant in an orally administered solid dispersing form designed to disintegrate rapidly in the oral cavity.

2. A vaccine composition according to Claim 1 wherein the antigen is encapsulated in a material designed to enhance its absorption.

10 3. A vaccine composition according to Claim 2 wherein the antigenic preparation is encapsulated in polymeric particles, or absorbed onto polymeric particles.

4. A vaccine composition according to Claim 3 wherein the polymeric particle is a poly(lactic acid) or a poly(lactide-co-glycide), or a combination thereof.

5. A vaccine composition according to Claim 3 wherein the polymeric particle is latex.

6. A vaccine composition according to any  
20 preceding Claim including a mucoadhesive substance.

7. A vaccine composition according to any preceding Claim in which the solid dispensing form is a low density matrix tablet or water.

8. A vaccine composition according to Claim 7 wherein the low density matrix is formed by removal of solvent by lyophilisation from a frozen suspension.

9. A vaccine composition according to Claim 7 wherein the low density matrix is formed by removal of solvent from a frozen suspension by contact with a  
30 second solvent, in which the matrix forming materials are insoluble.

10. A vaccine composition according to Claim 7 wherein the low density matrix is formed by compacting finely divided extruded materials.

35 11. A vaccine composition according to Claim 7 wherein the low density matrix is formed by loosely compacting particles formed by spray-coating, spray-

drying, lyophilisation, spray-chilling, coacervation, or fluid-bed drying.

12. A vaccine composition according to Claim 7 wherein the low density matrix is formed by gelling a suspension and then removing solvent by drying.

13. A vaccine composition according to any preceding Claim wherein the solid dispensing form disintegrates within one minute in the oral cavity.

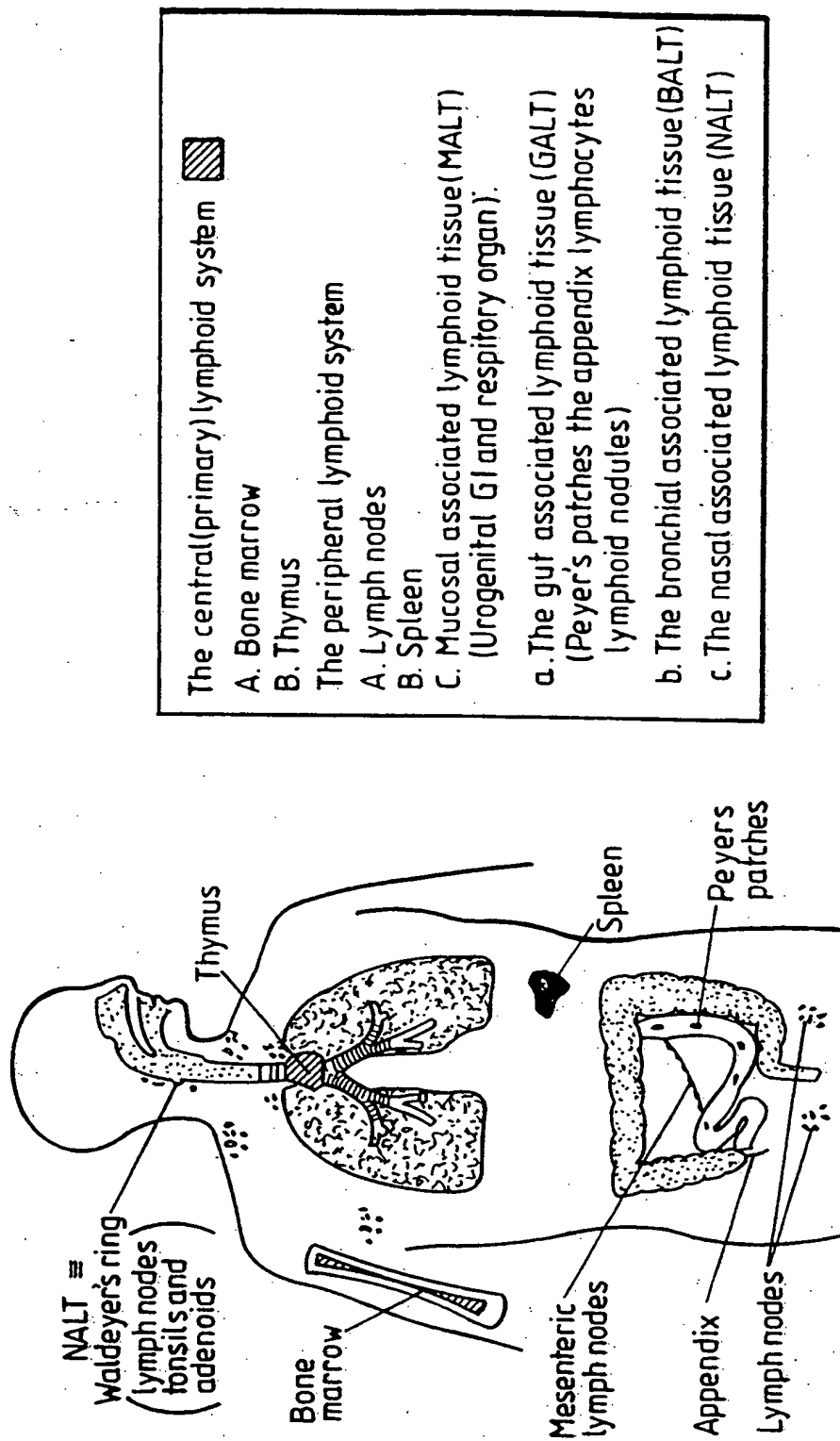
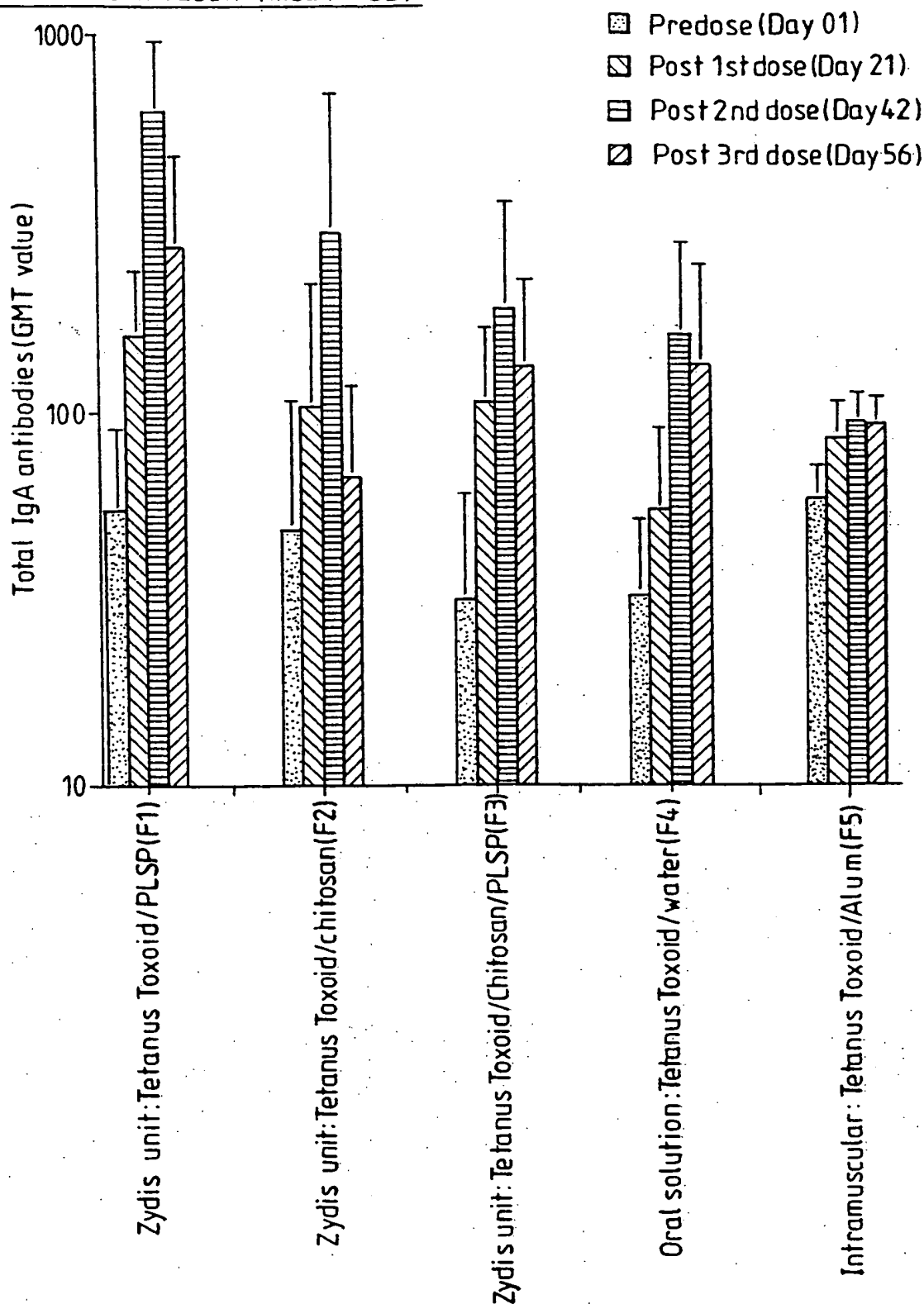


Fig.1.

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Fig.2.

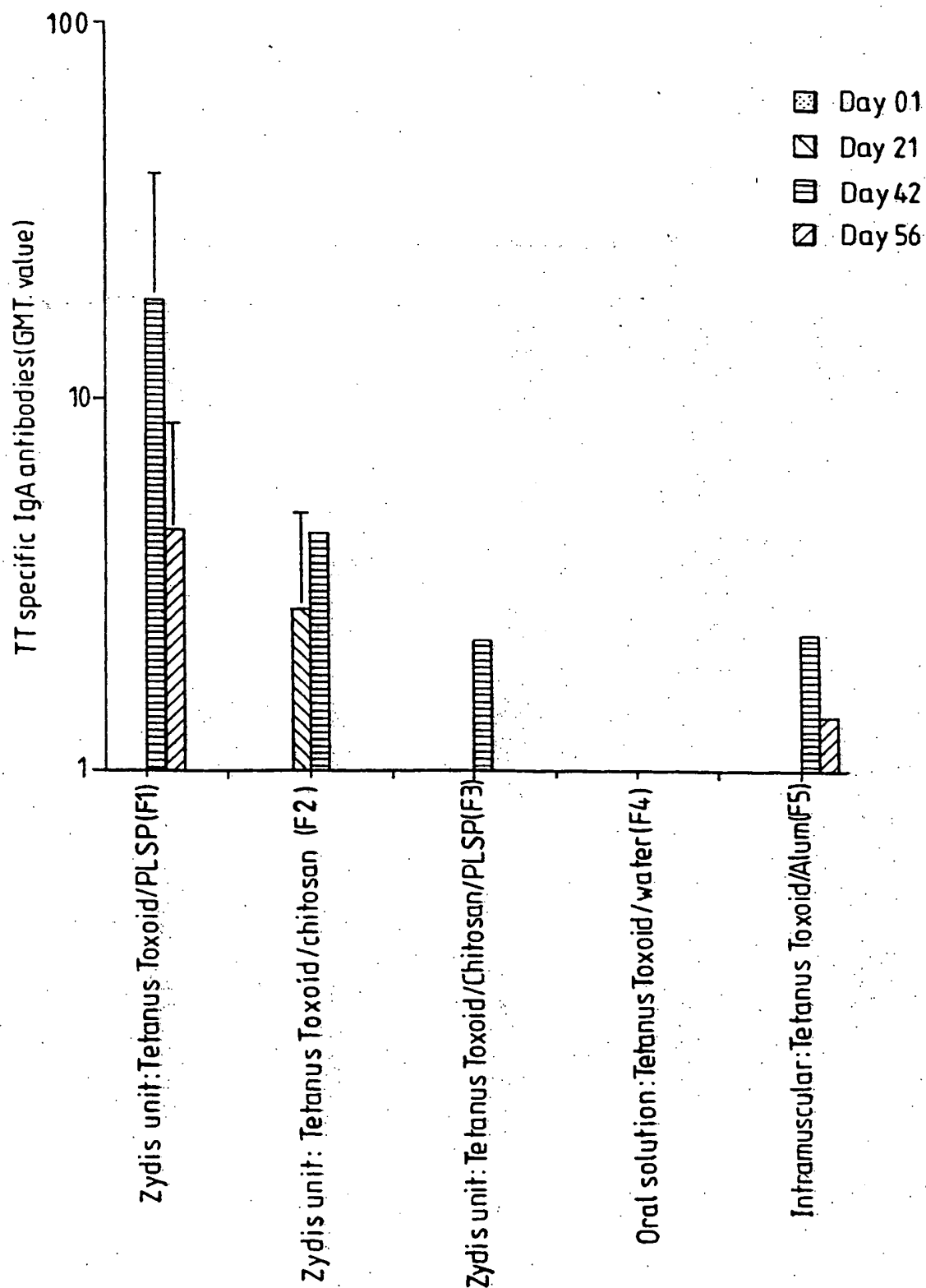
Geometric mean titre (GMT) values of total IgA antibodies in saliva samples after the oral or intramuscular administration of Tetanus Toxoid (TT) from various formulations in rabbit (mean  $\pm$  SD)



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Fig.3.

Geometric mean titre (GMT) values of TT specific IgA antibodies in saliva samples after the oral or intramuscular administration of Tetanus Toxoid (TT) from various formulations in rabbits mean  $\pm$  SD





# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 98/03209

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K39/00 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 548 022 A (WYETH JOHN & BROTHER LTD) 4 July 1979 cited in the application * whole document, noting especially page 2, lines 67-68 *	1-13
X	US 5 298 261 A (PEBLEY WALTER S ET AL) 29 March 1994 cited in the application * whole document, noting especially column 10, line 65 *	1-13
A	WO 94 20070 A (SECRETECH INC ;DUNCAN JACQUELINE D (US); SCHAFER DENNIS P (US)) 15 September 1994 see page 2, paragraph 3 - page 3, paragraph 1  -/-	1-13

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

20 January 1999

Date of mailing of the international search report

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Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Sitch, W

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 98/03209

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 21464 A (EMISPHERE TECH INC ;SANTIAGO NOEMI B (US); HAAS SUSAN (US); LEONE) 18 July 1996 see page 20, line 15 - page 25, line 10	1-13
A	MESTECKY J ET AL: "BIODEGRADABLE MICROSPHERES FOR THE DELIVERY OF ORAL VACCINES" JOURNAL OF CONTROLLED RELEASE, vol. 28, no. 1/03, 1 January 1994, pages 131-141, XP000435244 see page 131 see abstract see page 133, paragraph 5 - page 135, paragraph 1	1-13

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